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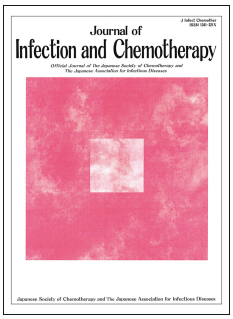

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Case report

Article title:

Successful treatment of proven coronavirus disease 2019-associated pulmonary aspergillosis with liposomal amphotericin B in a patient with bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplantation

Authors:

Yosuke Nakaya[1], Yasuhiro Nakashima[1], Naonori Harada[1], Koichi Yamada[2], Yosuke Makuuchi[1], Masatomo Kuno[1], Teruhito Takakuwa[1], Hiroshi Okamura[1], Satoru Nanno[3], Mitsutaka Nishimoto[1], Hideo Koh[1], Yu Nakagama[4], Yasutoshi Kido[4], Takayuki Kanno[5], Tadaki Suzuki[5], Hirohisa Nakamae[1], Hiroshi Kakeya[2], Masayuki Hino[1]

[1]Department of Hematology, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan

[2] Department of Infection Control Science, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan

[3]Department of Hematology, Osaka General Hospital of West Japan Railway Company, Osaka, Japan.

[4]Department of Parasitology and Research Center for Infectious Disease Sciences, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan

[5]Department of Pathology, National Institute of Infectious Diseases, Tokyo, Japan

Correspondence and E-mail address:

Yasuhiro Nakashima, ynakashima@omu.ac.jp

ORCID

Yosuke Nakaya 0000-0003-3337-1599

Masatomo Kuno 0000-0003-4548-147X

Mitsutaka Nishimoto 0000-0002-0388-3836

Hirohisa Nakamae 0000-0003-4203-990X

Authorship statement

All authors meet the International Committee of Medical Journal Editors (ICMJE) authorship criteria for this article.

Abstract

Coronavirus disease 2019 (COVID-19)-associated pulmonary aspergillosis (CAPA) is being increasingly recognized as a severe complication that contributes to poor prognoses among patients with COVID-19. However, little is known regarding the clinical course of CAPA with hematological malignancies, especially after allogeneic hematopoietic stem cell transplantation (HSCT). A 29-year-old woman was diagnosed with proven CAPA with an *Aspergillus fumigatus* identified by cultures of bronchoalveolar lavage and lung biopsy four years after haploidentical HSCT for acute myelogenous leukemia. She had been taking oral prednisolone for bronchiolitis obliterans syndrome that developed after HSCT. Although prolonged RT-PCR positivity for SARS-CoV-2 (133 days after the onset of COVID-19) without shedding of viable virus was observed, the COVID-19 was treated with favipiravir, remdesivir, dexamethasone, and enoxaparin. However, the CAPA did not respond to combination therapy, which included triazole (voriconazole, itraconazole, posaconazole) and echinocandin (caspofungin, micafungin), even though the *Aspergillus fumigatus* isolate was found to be susceptible to these agents in vitro. Nevertheless, a total of 16 weeks of liposomal amphotericin B (L-AMB) therapy led to a favorable response, and the patient was discharged from the hospital on day 213. This case provided essential experience of CAPA treated with L-AMB in a recipient with chronic respiratory disease after HSCT.

Keywords

COVID-19-associated pulmonary aspergillosis; SARS-CoV-2; Liposomal amphotericin B; Allogeneic hematopoietic stem cell transplantation; Bronchiolitis obliterans syndrome

Introduction

In March 2020, the World Health Organization declared Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a global pandemic. Since then, more than 526 million people have been infected, and 6.2 million deaths were recorded by the end of May 2022. Adult patients with hematological malignancies and COVID-19 have a higher risk of developing severe forms of the disease, and its mortality risk has been reported to be 34% [1]. Emerging reports have also highlighted poor prognoses in recipients of hematopoietic stem cell transplantation (HSCT), with mortality rates of 19%−33% and 22%−35% after autologous and allogeneic HSCT, respectively [2-4].

COVID-19-associated pulmonary aspergillosis (CAPA) is widely recognized as an additional factor contributing to shorter survival. A recent review analyzing eight cohort studies demonstrated that the incidence of CAPA was 3.3%−34.4% in critically ill patients with COVID-19, and all-cause mortality among patients with CAPA was significantly higher than that of non-CAPA patients [5]. Most studies investigating CAPA have been conducted in the setting of intensive care units and have included small numbers of patients with hematological malignancies. Therefore, less information is available regarding CAPA along with hematological cancers, particularly after HSCT.

Case report

A 29-year-old woman presented to our department with fever, shortness of breath, and persistent dry cough. Four years earlier, she had undergone HLA-haploidentical allogeneic HSCT from her farther with posttransplant cyclophosphamide for the treatment of acute myelogenous leukemia. While the leukemia went into complete remission, she developed bronchiolitis obliterans syndrome (BOS) 18 months after the HSCT, and combined therapy including prednisolone, clarithromycin, montelukast, and inhaled corticosteroid/long-acting β_2-agonist was started. Additionally, she had itraconazole for prophylaxis of invasive fungal infections. Given that the treatment showed a partial response, the prednisolone dosage was tapered from 40 mg per day to 12.5 mg every other day at the visit.

Given that an antigen test for SARS-CoV-2 was positive and that chest computed tomography (CT) demonstrated bilateral ground-glass opacities that were predominantly peripheral and basal in distribution, she was admitted to the isolation ward for COVID-19 treatment. On admission, the patient had a body temperature of 39.0°C, respiratory rate of 24 breaths per min, and an oxygen saturation of 95% using nasal oxygen at 1−2 L/min. Treatment was initiated with favipiravir, dexamethasone, and enoxaparin (for venous thromboembolism prophylaxis). Tazobactam/piperacillin and caspofungin, were additionally administered for possible bacterial and fungal coinfection. However, her respiratory condition deteriorated, and a chest CT on day 7 showed ground-glass opacities that extended to the central side, and multiple thick-walled cavities appeared in both lungs (Figure 1). We switched favipiravir to

remdesivir and also started oral voriconazole because a blood test detected elevated serum β-D glucan (31.4 pg/mL, normal range ≤ 20 pg/mL) and galactomannan (GM) levels (0.7, normal range ≤ 0.5), corresponding to a diagnosis of probable CAPA [6].

While RT-PCR for SARS-CoV-2 was consistently positive until day 133, the cycle threshold (Ct) gradually increased, and viral cultures performed on days 57, 72, and 133 detected no viable SARS-CoV-2 (Table 1). Antibodies targeting the SARS-CoV-2 spike receptor-binding domain (RBD), a correlate of viral neutralizability, were detectable on day 120, 122, and 133 (Abbott Diagnostics, Chicago, IL, USA) [7]. Thus, the clinical status relevant to COVID-19 was considered to be improving. Meanwhile, β-D glucan levels and cavitary lesions in both lungs were increasing, suggesting the progression of CAPA (Figure 1). A lung biopsy through bronchoscopy at the left B1 performed on day 72 only found inflammatory cell infiltration, including plasma cell, lymphocyte, neutrophil, and histiocyte-like cell, with no evident fungus body; however, a fungal culture of both bronchoalveolar lavage fluid (BALF) and lung tissue detected an *Aspergillus fumigatus* isolate (proven CAPA) susceptible to all antifungal drugs except for 5-fluorocytosine and fluconazole as per Clinical and Laboratory Standards Institute (CLSI) document M38-A2 (Table 2) [6, 8]. GM in BALF was high (index: 4.7). Although voriconazole trough levels were sustained within the therapeutic range (1−5 μg/mL), the patient had a persistent fever with a gradual increase in C-reactive protein (CRP) and β-D glucan levels (Figure 2). Other triazoles (itraconazole, posaconazole) combined with

micafungin did not improve the clinical findings despite their susceptibilities in vitro. Nonetheless, liposomal amphotericin B (L-AMB) (5.0 mg/kg/day) started from day 76 improved the prolonged fever, high levels of CRP, and β-D glucan, and cavitary lung lesions (Figure 1−2). L-AMB administration was discontinued after 4 weeks due to severe hypokalemia and moderate renal dysfunction; however, the CAPA flared up 4 weeks after the cessation in terms of recurrent fever and increase in CRP and β-D glucan levels (Figure 2). We therefore readministered L-AMB at a reduced dosage (2.5−3.0 mg/kg/day) under discreet monitoring and adequate potassium supplementation. L-AMB treatment could be continued without additional adverse events thereafter, and the patient was discharged from the hospital on day 213 without oxygen supplementation.

Discussion

During the COVID-19 pandemic, mycological examinations through bronchoscopy are challenging because they can increase the risk of nosocomial infection via potential exposure of dispersed aerosols to healthcare workers [9]. Most CAPA cases have therefore been categorized into putative rather than proven or probable CAPA [10]. To the best of our knowledge, only one case of CAPA following allogeneic HSCT has been reported to date [11]. The case involved a 19-year-old man with acute lymphoblastic leukemia who developed CAPA just 12 days after HSCT under primary prophylaxis for invasive fungal diseases with

posaconazole. Fortunately, the patient was successfully treated with L-AMB; however, he could not undergo bronchoscopic examination due to poor general condition and thrombocytopenia. Thus, the CAPA case was classified as “probable” due to the lack of mycological evidence. Our patient would therefore be the first “proven” case of CAPA after allogeneic HSCT. The breakthrough infection of CAPA under prophylaxis with triazole and the favorable response to L-AMB are common clinical aspects between these cases.

Previous studies have identified several risk factors associated with CAPA among patients with COVID-19: older age, chronic obstructive pulmonary disease, and long-term corticosteroid use [5]. In our case, the long-term use of oral prednisolone could also have contributed to the onset of CAPA.

Pulmonary aspergillosis in patients with chronic respiratory disease has an extremely high mortality [12]. Therefore, early and correct diagnosis followed by prompt antifungal therapy is important to enhance the prognosis in such patients. The benefit and the risk of exposure to SARS-CoV2 must be balanced; however, bronchoscopy in patients with COVID-19 should be considered whenever clinically indicated since the risk of viral transmission to health care workers is very low under appropriate infection control precautions [13]. BALF GM, in addition to serum GM, serves as an auxiliary diagnostic biomarker for pulmonary aspergillosis occurring in chronic respiratory disease [14]. In our case, timely bronchoscopy with BALF GM could help confirm a diagnosis of CAPA.

Persistent RNA shedding of SARS-CoV-2 detected by RT-PCR has been reported in several cases up to 230 days after symptom onset in COVID-19 [15]. In most cases, however, the persistent positivity of viral RNA does not correlate with infectivity because the duration of viable virus shedding is shorter than that of viral RNA. In general, the viable virus detected by cell culture ranged from −6 to 20 days after symptom onset [16]. However, the shedding of infective SARS-CoV-2 can persist for more than 20 days (maximum of 70 days) in patients with COVID-19 with hematological malignancies including transplant recipients and those undergoing cellular therapy [17-19]. In the event of prolonged PCR positivity, Ct values in RT-PCR can be a surrogate measure of transmission potential because the level inversely correlates with culturable SARS-CoV-2 [16]. For example, a Ct value ≥ 34 is considered to indicate a noninfectious state [20]. Detection of neutralizing antibodies also serves as an indicator of lower risk of shedding contagious SARS-CoV-2, although corticosteroid use decreases its neutralization titer against SARS-CoV-2 [21]. In our case, prolonged RT-PCR positivity and a low anti-RBD antibody titer could have reflected the patient's immunosuppressive status during corticosteroid therapy, while the correlation between Ct values in RT-PCR and negative viral cultures, together with the generation of neutralizing antibodies were in line with previous reports [16, 20, 21].

As for the treatment of CAPA in this case, triazoles (voriconazole, itraconazole, posaconazole) combined with echinocandins (caspofungin, micafungin) were ineffective

despite their susceptibility in laboratory testing, while L-AMB showed a favorable response. The mechanism of the discrepancies between laboratory susceptibility and clinical response of antifungal agents were unclear; however, a possible explanation might be the difference of tissue penetration among antifungal agents [22]. Voriconazole, recognized as a primary therapy for invasive pulmonary aspergillosis, exhibited better efficacy and safety than conventional AMB deoxycholate (AMB-d) in a randomized trial [23]. However, the median duration of AMB-d treatment in the study was much shorter than that of voriconazole (10 days vs. 77 days) because of greater adverse events in the AMB-d cohort [23]. Therefore, it is difficult to evaluate the true superiority in efficacy. L-AMB is a lipid formulation developed to reduce AMB-d toxicity while retaining its broad antifungal activities, although no comparative study has been conducted between voriconazole and L-AMB. When adverse effects are under control, substituting L-AMB for triazoles could be a better choice in clinically triazole-refractory CAPA cases even if the antifungal test shows triazole susceptibility.

In conclusion, our case provided valuable CAPA treatment experience in an allogeneic HSCT recipient. Given that chronic respiratory disease is a poor prognostic factor for patients with pulmonary aspergillosis, early and accurate diagnosis of CAPA is crucial for recipients with pulmonary complication after HSCT. Bronchoscopic examination with cultures of BALF and lung tissue, combined with BALF GM, should be considered for high-risk immunocompromised patients with suspected CAPA. If the treatment response to CAPA is

suboptimal, switching to L-AMB from other antifungal agents could be an effective therapeutic option irrespective of their drug susceptibilities in vitro.

Ethics approval

According to the guidelines of the Ministry of Health, Labour and Welfare in Japan, the approval of the Ethics Committee is not required for clinical case report. The Ethics Committee at Osaka Metropolitan University ruled that no formal ethical approval is required for reporting case study.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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Authors' contributions

Conceptualization: Yosuke Nakaya, Yasuhiro Nakashima; Microbiological examination: Yu Nakagama, Yasutoshi Kido, Takayuki Kanno, Tadaki Suzuki; Original draft preparation: Yosuke Nakaya; Review and editing: All authors

Conflict of Interest

Hideo Koh, Hirohisa Nakamae, Hiroshi Kakeya, and Masayuki Hino received honorarium from Sumitomo Dainippon Pharma Co., Ltd. Masayuki Hino received research funding from Sumitomo Dainippon Pharma Co., Ltd. The other authors declare that there is no conflict of interests.

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None

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Figure legend

Fig. 1.

Longitudinal changes in the chest computed tomography (CT) scans after admission. While the bilateral ground-glass opacities (*red arrows*) disappeared, the thick-walled cavities increased in size (*blue arrow*). However, the walls of these cavity lesions gradually thinned after starting treatment with liposomal amphotericin B on day 76 (*green arrow*).

Fig. 2.

Clinical course of the patient.

Abbreviations: BALF, bronchoalveolar lavage fluid; BT, body temperature; CPFG, caspofungin; CRP, C-reactive protein; GM, galactomannan; ITCZ, itraconazole; L-AMB, liposomal amphotericin B; MCFG, micafungin; TAZ/PIPC, tazobactam/piperacillin; PSCZ, posaconazole; VRCZ, voriconazole

Table 1 Results of time-series data associated with SARS-CoV-2

day	1	8	17	24	31	49	57	72	120	122	133	213
Antigen test	+								−			
RT-PCR		+	+	+	+	+	+			+	+	−
Ct value		NA	20.8	28.4	31.5	35.2	32.2			31.0	33.0	
Viral culture							−	−			−	
Antibody test (IgG)*									N: 1.6 S: 2041.8	N: 1.32 S: 1621.9	N: 1.45 S: 1557.0	

Abbreviations: Ct, threshold cycle; IgG, immunoglobulin G; NA, not available; RT-PCR, reverse transcription polymerase chain reaction;

* Antibody test was analyzed by Abbott Architect SARS-CoV-2 IgG & SARS-CoV-2 IgG II Quant methods. “N”, anti-nucleocapsid antibody test; “S”, anti-spike (receptor-binding domain) antibody test.

Table 2 Result of antifungal susceptibility testing of *Aspergillus fumigatus*

Antifungal agent	MIC (mg/L)
Amphotericin B	0.5
5-fluorocytosine	> 64
Fluconazole	> 64
Miconazole	2
Itraconazole	0.25
Voriconazole	1
Posaconazole	≤ 0.25
Micafungin	≤ 0.015*
Caspofungin	0.25*

* The antifungal end point for echinocandins were set as minimum effective concentration (MEC).

Abbreviations: MIC, minimum inhibitory concentration